

CLAIMS

What is claimed is:

1 – A compound binding the G-quadruplex structure of DNA or RNA, which
5 corresponds to the following general formula (IB):

nitrogen-containing aromatic ring possessing a nitrogen atom in quaternary form – (NR₃)p – CO- distribution agent – (CO)m – (NR'₃)q –X- aromatic or nonaromatic ring

10 (IB)

wherein m, p and q, which are identical or different, representing the integer 0 or 1,

wherein

- 15 • the nitrogen-containing aromatic ring possessing a quaternary atom is:
 - ◊ a quinoline optionally substituted with at least
 - one group N(Ra)(Rb) wherein Ra and Rb, are identical or different, are hydrogen or C1-C4 alkyl or
 - C1-C4 alkyl or alkoxy or
 - ◊ wherein the nitrogen atom is quaternized with a C1-C4 alkyl chain optionally substituted with hydroxyl, carboxyl, C1-C4 alkoxy, C1-C4 alkylthio, amino, C1-C4 alkylamino or C1-C4 dialkylamino for each alkyl group,
 - the aromatic or nonaromatic ring is:
 - ◊ a quinoline optionally substituted with at least
 - one group N(Ra)(Rb) wherein Ra and Rb, are identical or different, are hydrogen or C1-C4 alkyl or
 - C1-C4 alkyl or alkoxy or
 - ◊ a quinoline possessing a nitrogen in quaternary form or
 - ◊ a benzimidine or
 - ◊ a pyridine or
 - ◊ a phenyl nucleus optionally substituted with halogen, C1-C4 alkoxy, cyano, or carbonylamino wherein said carbonylamino group is optionally substituted with one or

- more substituents independently selected from the group consisting of C1-C4 alkyl, guanyl, C1-C4 alkylthio, amino, C1-C4 alkylamino, a C1-C4 dialkylamino for each alkyl group, nitro, C1-C4 alkyleneamino and C2-C4 alkenyleneamino or
- 5 ◊ a mono- or bi- or tricyclic aromatic or nonaromatic heterocyclic nucleus containing 0 to 2 heteroatoms per ring provided that at least one heteroatom has at least one ring optionally substituted with one or more substituents selected from the group consisting of C1-C4 alkyl, C1-C4 alkylene and C2-C4 alkenylene, and when the heteroatom, is nitrogen, it may be optionally in quaternary form
- 10 • R₃ and R'₃, which are identical or different, are independently hydrogen, C1-C4 alkyl or an aralkyl radical wherein the alkyl part is C1-C4
- 15 • X represents a single bond, C1-C4 alkyl, C2-C4 alkenyl, a C2-C4 alkynyl or phenyl
- 20 • the distribution agent is:
- ◊ a 5- or 6-membered heterocyclic radical containing a sulfur, oxygen or nitrogen
- ◊ a phenyl or
- ◊ a diazine or triazine group,
- 25 wherein heterocyclic, phenyl, diazine or triazine groups are optionally substituted with one or more substituents chosen from halogen, C1-C4 alkyl, thio, oxy or amino substituents wherein any such substituents are optionally substituted with one or more alkyl chains containing 1 to 4 carbon atoms,
- 30 it being understood that for the products of formula (IB) in which X represents a single bond, when the distribution agent represents phenyl optionally substituted with NH₂, m, p and q represent 1 and R₃ and R'₃ represent hydrogen, then the nitrogen-containing aromatic ring and the aromatic ring do not both represent a quinoline which is unsubstituted or substituted on its nitrogen atom with an alkyl radical containing 1 to 6 carbon atoms,
- 35 or one of its salts and when the distribution agent represents a triazine and p and q both represent the integer 1 then m does not represent the integer 0,

said products of formula (IB) may be in all the possible isomeric forms, such as the racemic, enantiomeric and diastereoisomeric forms, and the addition salts with inorganic or organic acids or with inorganic or organic bases of said
5 products of formula (IB).

2 – The compound according to claim 1 which binds to the G-quadruplex structure of telomers.

3 – The compound according to claim 1 which is a highly specific ligand for G-quadruplex DNA.

10 4 – The compound according to claim 1, wherein the heterocyclic groups among which the distribution agent may be chosen are thienyl and pyridyl groups.

15 5 - The compound according to claim 1, wherein the distribution agent is chosen from the heterocyclic groups pyridyl, thienyl, a phenyl, a diazine or a triazine.

6 – The compound according to claim 5, wherein the diazine groups are pyrazines.

20 7 – The compound according to claim 1, wherein the distribution agent is meta-disubstituted with the groups “nitrogen-containing aromatic ring possessing a nitrogen atom in quaternary form – (NR₃)p – CO” and “(CO)m – (NR'₃)q – aromatic or nonaromatic ring” as defined in claim 1 and wherein the distribution agent is, optionally substituted by halogen.

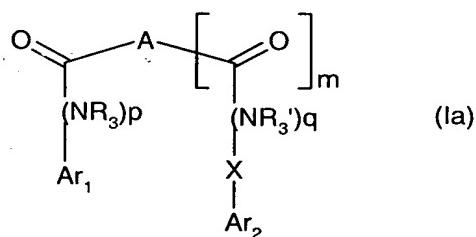
8 – The compound according to claim 1, wherein the heterocycle in quaternary form is a quinoline.

25 9 – The compound according to claim 1, wherein the distribution agent represents a pyridine which is 2,6-disubstituted or a pyridazine which is 2-6-disubstituted with the groups “nitrogen-containing aromatic ring possessing a quaternary nitrogen atom in quaternary form – (NR₃)p – CO” and “(CO)m – (NR'₃)q – aromatic or nonaromatic ring” and wherein the quaternized
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heterocycle is an N-methylquinolinium and wherein the distribution agent is, , optionally substituted by halogen.

- 10 – The compound according to claim 1, wherein p and q are the integer 1.
 5 11 – The compound according to claim 1, wherein m, p and q are the integer 1.

12 – The compound according to claim 1, having the formula (la)



wherein m, p and q, are identical or different, are integers from 0 to 1

10 wherein

- A is:
 - ◊ a 5- or 6-membered heterocyclic radical containing a sulfur, oxygen or nitrogen
 - ◊ a phenyl or
 - ◊ a diazine or triazine group,

15 wherein the heterocyclic, phenyl, diazine or triazine radicals are optionally substituted with one or more substituents chosen from halogen, C1-C4 alkyl, thio, oxy or amino substituents wherein any such substituents are optionally substituted with one or more short-chain alkyl chains containing 1 to 4 carbon atoms,

- Ar₁ and Ar₂, may be the same or different

20 wherein Ar₁ and Ar₂ are identical, they are a nitrogen-containing aromatic ring possessing a quaternary atom represented by a quinoline optionally substituted with at least

- one group N(Ra)(Rb) wherein Ra and Rb, are identical or different, are hydrogen or C1-C4 alkyl or
- one C1-C4 alkyl or alkoxy group or

◊ wherein the nitrogen atom is quaternized with a C1-C4 alkyl chain optionally substituted with a hydroxyl, carboxyl, C1-C4 alkoxy, C1-C4 alkylthio, amino, C1-C4 alkylamino or C1-C4 dialkylamino for each alkyl group,

5 wherein Ar₁ and Ar₂ are different

Ar₁ represents one of the above possibilities and Ar₂ represents

* phenyl optionally substituted with halogen, C1-C4 alkoxy, cyano, carbonylamino wherein said carbonylamino is optionally substituted with one or more substituents independently selected from the group consisting of C1-

10 C4 alkyl, a guanyl, a C1-C4 alkylthio, amino, C1-C4 alkylamino, C1-C4 dialkylamino for each alkyl group, nitro, C1-C4 alkyleneamino and C2-C4 alkenyleneamino or

* a benzamidine

* a pyridyl

15 * a mono- or bi- or tricyclic aromatic or nonaromatic heterocyclic nucleus containing 0 to 2 heteroatoms per ring provided that at least one heteroatom has at least one ring optionally substituted with one or more substituents independently selected from C1-C4 alkyl C1-C4 alkylene and C2-C4 alkenylene,

20

- R₃ and R'₃, are identical or different, are independently hydrogen, C1-C4 alkyl or aralkyl wherein alkyl is C1-C4,
- X is a single bond, or C1-C4 alkyl, a C2-C4 alkenyl, alkynyl or phenyl ,

25

said compound of formula (Ia) may be in all the possible isomeric forms, such as the racemic, enantiomeric and diastereoisomeric forms, and the addition salts with inorganic or organic acids or with inorganic or organic bases of said compound of formula (Ia).

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13 – The compound of formula (Ia) according to claim 12 wherein X is C1-C4 alkyl, the other substituents of the compound of formula (Ia) being as defined in claim 12,

35 said compound of formula (Ia) may be in all the possible isomeric forms, such as the racemic, enantiomeric and diastereoisomeric forms, and the addition

salts with inorganic or organic acids or with inorganic or organic bases of said compound of formula (Ia).

14 – The compound according to claim 12, wherein A is chosen from the heterocyclic groups, pyridyl, or thieryl, a phenyl, a diazine or a triazine.

5 15 – The compound according to claim 14, wherein the diazine groups which A can represent are pyrazines.

16 – The compound according to claim 12, wherein A is meta-disubstituted with the groups “nitrogen-containing aromatic ring possessing a nitrogen atom in quaternary form – (NR₃)p – CO” and “(CO)m – (NR'₃)q – aromatic or 10 nonaromatic ring”, and wherein A is, optionally substituted by halogen.

17 - The compound according to claim 12, wherein the heterocycle in quaternary form is a quinoline.

18 – The compound according to claim 12, wherein A represents a pyridine 15 which is 2,6-disubstituted or a pyridazine which is 2-6-disubstituted with the groups “nitrogen-containing aromatic ring possessing a quaternary nitrogen atom in quaternary form – (NR₃)p – CO” and “(CO)m – (NR'₃)q – aromatic or nonaromatic ring” and wherein the quaternized heterocycle is an N-methylquinolinium, and wherein A is optionally substituted by halogen.

20 19 – The compound according to claim 12, wherein m, p and q are the integer 1.

20 - The compound according to claim 12, wherein p and q are the integer 1.

21 – The compound according to claim 12, wherein Ar₂ is independently 25 selected from the group consisting of 4-amino- or 4-methylamino-, 4-dimethylamino- or 4-alkoxy-quinolyl and–quinolinium wherein said quinolinium is optionally substituted with one or two methyl groups.

22 – The compound according to claim 12, wherein R₃ and R'₃ are hydrogen.

23 – The compound according to claim 1 which is selected from the group 30 consisting of:

- bis[(1-methylquinolinio-6-yl)amido]-2,6-pyridinedicarboxylic acid diiodide
 - 2-[(1-methylquinolinio-6-yl)amido]-6-[(4-dimethylamino-1-methylquinaldinio-6-yl)amido]-2,6-pyridinedicarboxylic acid diiodide
 - bis[(1-methylquinolinio-6-yl)amido]-2,6-pyrazinedicarboxylic acid diiodide
- 5 - bis[(1-methylquinolinio-6-yl)amido]-1,3-benzenedicarboxylic acid diiodide
- bis[(1-methylquinaldinio-6-yl)amido]-2,6-pyridinedicarboxylic acid diiodide
 - 2-[(1-methylquinolinio-6-yl)amido]-6-[(4-aminoquinaldinio-6-yl)amido]-2,6-pyridinedicarboxylic acid iodide, isolated in its imino tautomeric form below:
 - bis[(1-methylquinaldinio-6-yl)amido]-2,6-benzenedicarboxylic acid diiodide
- 10 - bis[(1-methylquinolinio-6-yl)amido]-2,4-pyridinedicarboxylic acid diiodide
- 2-[(1-methylquinolinio-6-yl)amido]-6-[(1-methylquinolinio-3-yl)amido]-2,6-pyridinedicarboxylic acid iodide
 - 2-[(1-methylquinolinio-6-yl)amido]-6-[(1-methylquinolinio-5-yl)amido]-2,6-pyridinedicarboxylic acid iodide
- 15 - bis[(1-methylquinolinio-3-yl)amido]-2,6-pyridinedicarboxylic acid diiodide
- 2-[(1-methylquinolinio-6-yl)amido]-6-[2-(1-methylpiperidinio-1-yl)ethylamido]-2,6-pyridinedicarboxylic acid diiodide
 - 2,6-pyridinedicarboxylic acid 2-[(1-methylquinolinio-3-yl)amide]-6-[quinolin-3-yl]amide] iodide
- 20 - 2,6-pyridinedicarboxylic acid 2-[(1-methylquinolinio-3-yl)amide]-6-[1-(2-hydroxyethyl)quinolinio-3-yl]amide] iodide, and
- 4-bromo-2,6-pyridinedicarboxylic acid bis[(1-methylquinolinio-3-yl)amide] diiodide,
- or
- 25 said compounds may be in all the possible isomeric forms, such as the racemic, enantiomeric and diastereoisomeric forms, and the addition salts with inorganic or organic acids or with inorganic or organic bases of said compound.
- 24 – The compound according to claim 1, which is selected from the group consisting of::
- 30
- bis[(1-methylquinolinio-6-yl)amido]-2,6-pyridinedicarboxylic acid diiodide
 - 2-[(1-methylquinolinio-6-yl)amido]-6-[(4-dimethylamino-1-methylquinaldinio-6-yl)amido]-2,6-pyridinedicarboxylic acid diiodide
 - bis[(1-methylquinolinio-6-yl)amido]-2,6-pyrazinedicarboxylic acid diiodide
- 35 - bis[(1-methylquinolinio-6-yl)amido]-1,3-benzenedicarboxylic acid diiodide

- bis[(1-methylquinolinio-6-yl)amido]-2,6-pyridinedicarboxylic acid diiodide
 - 2-[(1-methylquinolinio-6-yl)amido]-6-[(4-aminoquinolinio-6-yl)amido]-2,6-pyridinedicarboxylic acid iodide, isolated in its imino tautomeric form below:
 - bis[(1-methylquinolinio-6-yl)amido]-2,6-benzenedicarboxylic acid diiodide
 - 5 - bis[(1-methylquinolinio-6-yl)amido]-2,4-pyridinedicarboxylic acid diiodide
 - 2-[(1-methylquinolinio-6-yl)amido]-6-[(1-methylquinolinio-3-yl)amido]-2,6-pyridinedicarboxylic acid iodide
 - 2-[(1-methylquinolinio-6-yl)amido]-6-[(1-methylquinolinio-5-yl)amido]-2,6-pyridinedicarboxylic acid iodide
 - 10 - bis[(1-methylquinolinio-3-yl)amido]-2,6-pyridinedicarboxylic acid diiodide
 - 2,6-pyridinedicarboxylic acid 2-[(1-methylquinolinio-3-yl)amide]-6-[quinolin-3-yl]amide] iodide
 - 2,6-pyridinedicarboxylic acid 2-[(1-methylquinolinio-3-yl)amide]-6-[1-(2-hydroxyethyl)quinolinio-3-yl]amide] iodide, and
 - 15 - 4-bromo-2,6-pyridinedicarboxylic acid bis[(1-methylquinolinio-3-yl)amide] diiodide,
- or
- said compounds may be in all the possible isomeric forms, such as the racemic, enantiomeric and diastereoisomeric forms, and the addition salts
- 20 with inorganic or organic acids or with inorganic or organic bases of said compounds.

25 –The compound according to claim 1 which is 2-[(1-Methylquinolinio-6-yl)amido]-6-[2-(1-methylpiperidinio-1-yl) ethylamido]-2,6-pyridinedicarboxylic acid diiodide

wherein said compound may be in all the possible isomeric forms, such as the racemic, enantiomeric and diastereoisomeric forms, or the addition salts with inorganic or organic acids or with inorganic or organic bases.

30 26 – The compound according to claim 1, which has a telomerase inhibiting activity.

27 – The compound according to claim 1, which has an anticancer activity.

35 28 – The compound according to claim 1 having the formula (IB) and their prodrugs, said compound of formula (IB) may be in all the possible isomeric forms, such as the racemic, enantiomeric and diastereoisomeric forms, and

the addition salts with pharmaceutically acceptable inorganic or organic acids or with inorganic or organic bases of said compounds of formula (IB).

- 29 – The compound according to claim 12 having the formula (Ia) and their prodrugs, said compound of formula (Ia) may be in all the possible isomeric forms, such as the racemic, enantiomeric and diastereoisomeric forms, and the addition salts with pharmaceutically acceptable inorganic or organic acids or with inorganic or organic bases of said compound of formula (Ia).
- 10 30 – A pharmaceutical composition comprising an effective cancer inhibiting amount of a compound of claim 1.
- 15 31 – The pharmaceutical composition according to claim 30, further comprising active ingredients of other chemotherapy medicaments against cancer.
- 32 – A therapeutic combination comprising a compound according to claim 1 and another anticancer compound.
- 20 33. – The combination as claimed in claim 32, wherein the anticancer compound is selected from the group consisting of alkylating agents, platinum derivatives, antibiotics, antimicrotubule agents, anthracyclines, groups I and II topoisomerases, fluoropyrimidines, cytidine analogs, adenosine analogs, various enzymes and compounds such as L-asparaginase, hydroxyurea, trans-retinoic acid, suramin, irinotecan, topotecan, dextrazoxane, amifostin, herceptin and the estrogen and androgen hormones, and antivascular agents.
- 25 34. – The combination according to claim 33, wherein each of the compounds or treatments is administered simultaneously, separately or sequentially.
35. – A therapeutic combination comprising a compound according to claim 1 and of radiation.
- 30 36– The combination according to claim 35, wherein each of the compounds or treatments is administered simultaneously, separately or sequentially

37. – A method of treating a disease selected from the group consisting of cancers, genetic diseases and pilosity diseases which comprises administering to a patient in need of said treatment an effective amount of a compound according to claim 1 having the formula (IB) or a pharmaceutically acceptable salt thereof.
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38. – The method according to claim 37 wherein the disease is cancer.
39. – The method according to claim 38 wherein said cancer is selected from the group consisting of cancer of the breast, stomach, colon, lungs, ovaries, uterus, brain, kidney, larynx, lymphatic system, thyroid, urogenital tract, tract including vesicle and prostate, bones, pancreas, and melanomas.
- 10
40. – The method according to claim 39 wherein said cancer is cancer of the breast, colon or lungs.
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- 41.– The method according to claim 37 wherein said genetic diseases are selected from the group consisting of Bloom's syndrome, Werner's syndrome, Rothmund-Thomson syndrome and ataxia telangiectasia syndrome.
- 20
42. – The method of claim 37 wherein said pilosity disease is hyperpilosity.